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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional): 204,940

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on December 24, 2009

Signature: Jay S. Cinamon

Typed or printed name: Jay S. Cinamon

Application Number	Filed
09/743,333	February 21, 2001

First Named Inventor: Lanfranco CALLEGARO

Art Unit	Examiner
1618	FUBARA, B.M.

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- ☐ applicant/inventor.
- ☐ assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- ☑ attorney or agent of record. Registration number 24,156.
- ☐ attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____

Jay S. Cinamon
Signature

Jay S. Cinamon
Typed or printed name

212-885-9232
Telephone number

December 24, 2009
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT	:	CALLEGARO et al.	EXAMINER	: FUBARA, B.M.
SERIAL NO.	:	09/743,333	ART UNIT	: 1618
FILED	:	February 21, 2001	CONFIRM NO.:	9321
FOR		BIOCOMPATIBLE AND BIODEGRADABLE COMPOSITIONS CONTAINING HYALURONIC ACID AND THE DERIVATIVES THEREOF FOR THE TREATMENT OF ULCERS IN THE DIGESTIVE APPARATUS		

December 24, 2009

STATEMENT OF FILING BY EXPRESS MAIL 37 CFR § 1.10
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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Mail Stop - AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Appellants request review of the second, non-final rejection of June 25, 2009 in the above-identified application.

When reference is made hereinafter to pages of the publication, it is to International Application No. WO 00/01394.

The review is requested for the reasons stated below.

Claims 25-32 and 34-51 are pending and stand rejected. Briefly, Claim 25 relates to a process for the preparation of a biological material for the treatment of ulcers, lesions and diverticula of the digestive and gastrointestinal apparatus, which comprises seeding and growing enterocytes optionally together with fibroblasts, mesenchymal cells, mature cells and/or epithelial cells on a bidimensional perforated membrane or on a bidimensional continuous membrane consisting essentially of at least one hyaluronic acid or a derivative thereof thereby obtaining morphologically differentiated enterocytes as confirmed by the presence of microvilli, whereas the product claims 34 and 39-51 refer to said biological material.

Claims 25-32 and 34-51 stand rejected under 35 U.S.C. §112 and also under 35 U.S.C. §103(a) as being obvious over Valentini et al. (US 5,939,323), over Dorigatti et al. (WO 94/17837) in view of Valentini et al. (US 5,939,323), and over Soranzo et al. (WO 96/33750) in view of Valentini et al. (US 5,939,323). These rejections represent clear errors by the Examiner which should be reviewed.

1. Rejection under 35 U.S.C. §112

According to the outstanding Office Action, at page 3, paragraph 5, the Examiner states, "The amended claims have recited seeding and growing enterocytes. But the specification as filed does not envision seeding enterocytes."

Appellants disagree with this conclusion since, indeed, enterocytes are well supported in the as-filed application, for example, at page 6, lines 7-9. Furthermore, it is well known to one of ordinary skill in the art that intestinal cells spontaneously differentiate into enterocytes, which are typical of the mature intestinal epithelium.

However, it should be noted that in the Office Action dated October 1, 2008, page 7, with reference to the submitted Declaration, the Examiner asserted that the pending claims recited "generic intestinal cells and not enterocytes".

However, it should be noted that in the Office Action dated October 1, 2008, page 7, with reference to the submitted Declaration, the Examiner asserted that the pending claims recited "generic intestinal cells and not enterocytes". Therefore, Appellants decided to follow the Examiner's indication by substituting "enterocytes" in claim 25 for "intestinal cells", even though the meaning of the first expression was preferable to Appellants, being that enterocytes are indeed intestinal absorptive cells.

Therefore, the new matter rejection is improper and should be reversed.

Furthermore, the Examiner asserts that the pending Claims are indefinite for failing to particularly point out the boundaries of the protection sought for the HA derivatives.

Appellants disagree with this conclusion since according to MPEP §2111, the pending claims must be "given their broadest reasonable interpretation consistent with the specification." (The Federal Circuit's en banc decision in Phillips v. AWH Corp., 415 F.3d 1303, 75 USPQ2d 1321 (Fed. Cir. 2005)). In this case, the HA derivatives are clearly defined at page 4, lines 6-31. Therefore, the broadest reasonable interpretation of the claims is consistent with the interpretation that those skilled in the art would reach, (see *In re Cortright*, 165 F.3d 1353, 1359, 49 USPQ2d 1464, 1468 (Fed. Cir. 1999)), because the skilled person can readily and would undoubtedly, refer to the list provided in the specification in order to understand the scope of the expression "HA derivative", as well as to dependent claims 26-32.

It should be noted that the Examiner never raised this rejection previously, even though the expression has been present since the filing of the application.

Therefore, the rejection for indefiniteness is also improper and should be reversed.

2. Rejection under 35 U.S.C. §103(a) as being obvious over Valentini et al. (US 5,939,323)

The Examiner states that "Valentini et al. describes that derivatives of hyaluronic acid are employed as raw material to fabricate porous, degradable scaffolds for medical purposes such as tissue repair and reconstruction and wound healing" and that "specifically discloses that the scaffolds can have virtually any size, thickness and shape having various porosities and pore size (column 4, lines 36-38)". Furthermore, the Examiner states that "scaffolds can be seeded with cells such as ... intestinal cells (column 8, lines 1-6)". The Examiner thus concludes that "the perforated membrane of the claims read on the porous scaffold of Valentini, which scaffold can also be a membrane", while acknowledging that Valentini does not disclose a 2-D matrix.

The Examiner then adds that "taking the general teaching of Valentini as regards the design and use of scaffold of any shape and structure and size, one having ordinary skill in the art at the time the invention was made would have reasonable expectation of success that intestinal cells seeded on the 3-D matrix or any other structural matrix including 2-D matrix or continuous matrix will grow. The prior art and the claimed invention achieve the same result of growing intestinal cells on hyaluronic acid matrix. There is no demonstration that intestinal cells cannot be seeded on the 3-D matrix of Valentini."

Moreover, the Examiner, in responding to Appellants' previous arguments, stated that "the language of perforated does not exclude the porous structure of Valentini and, basically, a perforated membrane is porous" and that "neither Annex 1, Annex 2 nor Annex 3 categorically states that a perforated material is non-porous".

By contrast, in Appellants' view, the Examiner has ***arbitrarily isolated*** sentences from Valentini et al. in order to conveniently lead to the claimed invention. This is a clear case of hindsight reconstruction of the claimed invention.

As a matter of fact, Valentini et al. at column 4, lines 30-38, teach that:

> The invention involves three-dimensional biodegradable scaffolds of hyaluronic acid derivatives for tissue reconstruction and repair. The porous scaffold has interconnected pores that permit cells to grow into the scaffold, preferably completely penetrating the scaffold with cells, and thereby, eventually replacing the scaffold with tissue. The scaffold can be fabricated to be virtually any shape, size or thickness, and can be produced to various porosities and pore sizes, depending upon the application. The scaffold is degradable,

Therefore, the sentence where "the scaffolds can have virtually any size, thickness and shape having various porosities and pore size" is expressly and unambiguously referring to the three-dimensional scaffolds of the immediately preceding sentence in the same paragraph. This is abundantly clear when considering the later statement at lines 45-46 where it is specified that "void volumes can range from 40-90% of the scaffolds".

Thus, one of ordinary skill in the art reading this document is no doubt aware of the fact that Valentini et al. ***only refer to 3-D scaffolds***, even more so in view of the fact that the required pores, i.e. void volumes, are ***unambiguously 3-D cavities***.

The Examiner states that Valentini et al. suggest that the scaffold can be a bidimensional membrane, in view of the fact that said document discloses to place the scaffold on a membrane insert!

Appellants wonder why the person of ordinary skill would have read this as posited by the Examiner. Again, Appellants are convinced that this is the result of an ***ex post facto analysis*** made by the Examiner having derived her knowledge solely from the claimed invention.

Indeed, the skilled person would have never misinterpreted this prior art document as has been surprisingly done by the Examiner. As a matter of fact, Valentini et al. expressly and unambiguously teach as follows:

1) the scaffolds must be "a three dimensional structure of interconnected pores which permits cell ingrowth and, eventually, tissue replacement of the scaffold" (column 2, lines 54-56);

2) the method for forming said scaffolds requires the use of a pore forming agent;

3) "In one particularly preferred embodiment, the pore forming agent is particles having a diameter between 10-1000 μm with optimal tissue ingrowth at 106 and 600 μm" (column 2, lines 56-59);

4) pores are void volumes in the scaffolds (column 4, lines 45-47).

From the above essential features, it is evident that the skilled person is taught to always configure a 3-D scaffold having interconnected pores where the ingrowth of cells takes place in order to succeed in repairing damage, including damage to visceral organs.

The requirement of a 3-D scaffold is even more evident when considering that the pores are 3-D cavities that must be present in said scaffolds. Therefore, when Valentini et al. refer to the possibility to have any shape and structure and size, this is always to be understood ***as any shape and structure and size of 3-D scaffolds having interconnected pores***.

Now, Appellants wonder how would the skilled person be motivated to modify the teaching of Valentini et al. in the direction of the claimed invention, **when all of the requirements** needed by the Valentini's scaffolds teach away **from the claimed invention** and when the Examiner has acknowledged that Valentini does not disclose a 2-D matrix?

Even more so, how would the ordinary skilled person possibly consider a 2-D matrix, when he/she is taught to necessarily have a porous structure and the pores are unambiguously known to be 3-D cavities, i.e. void volumes?

In this regard, how can the Examiner possibly state that "the perforated 2-D membrane read on the porous 3-D scaffold of Valentini", without acknowledging that this is an evident instance of hindsight?

As reported above, the Examiner states that "the language of perforated does not exclude the porous structure of Valentini and, basically, a perforated membrane is porous" and that "neither Annex 1, Annex 2 nor Annex 3 categorically states that a perforated material is non-porous". This assertion is absolutely contradictory since a bidimensional membrane necessarily does not have the physical possibility to be porous, ***as the third dimension is negligible by definition***! Therefore, how can it be that bidimensional openings in a bidimensional perforated membrane (see Annex 5 of the previous response) read on pores, when it is commonly known that pores are 3-D cavities?

It is clear that the expectations of success indeed fall flat when the teaching of Valentini et al. is not followed, i.e. when no porosity on a necessarily 3-D scaffold is provided, also in the case of intestinal cells. Thus, how could the skilled person, at the time the invention was made, believe he/she would succeed in growing enterocytes on a

bidimensional membrane that necessarily does not have the physical possibility to be porous, as the third dimension is negligible by definition, and thus does not provide the cavities where the ingrowth of cells could take place?

As a matter of fact, **the claimed biological material comprises the bidimensional membrane allowing the enterocytes to grow only bidimensionally and this is not possible with the porous 3-D scaffold of Valentini et al., wherein the cells are taught to grow within the suitably provided pores.**

Furthermore, the Examiner states that the Declaration of Mrs. Anna Zanellato is not commensurate with the Claims since specific cells derived from $CaCO_2$ cell lines were used and not enterocytes.

This is definitely groundless, since the skilled person at the time the invention was made clearly knew that said cell line derives from intestinal tumours and are commonly used in *in vitro* assays to predict the absorption rate of candidate drug compounds across the intestinal epithelial cell barrier, as is well-explained at page 6, lines 7-9, of the instant specification.

Therefore, all of the results as set forth in said Declaration are proper and further demonstrate that the claimed combination of features is neither suggested nor motivated at all by the teaching of Valentini et al.

Thus, for at least the above reasons, the claims clearly distinguish over Valentini et al. and the § 103(a) obviousness rejection should be reversed since the Examiner has not established a case of *prima facie* obviousness by a preponderance of the evidence.

3. Rejection under 35 U.S.C. §103(a) as being obvious over Valentini et al. (US 5,939,323) in view of Dorigatti et al. (WO 94/17837)

Dorigatti et al. disclose multilayer non-woven tissues having a minimum of 2 to 4 layers, wherein a layer that comes into contact with the skin is made of a hyaluronic acid derivative. These multilayer non-woven tissues are used in dermatology, "in medical/pharmaceutical field to cover the skin" (page 6, lines 5), thus they are used for external purposes.

Appellants, therefore, wonder why the skilled person would have even contemplated the possibility of combining Valentini et al. with Dorigatti et al., when the latter clearly does not pertain to the field of endeavour of the claimed invention, and even why the hypothetical combination of the teaching of a 3-D scaffold having interconnected pores and the teaching of multilayer non-woven tissues would result in a bidimensional membrane!

And also, even arbitrarily decontextualizing the information as the Examiner does, thus considering the sole hyaluronic acid derivative layer used in Dorigatti et al., it is disclosed that the same is non-woven, but nowhere in the document is it specified that said layer is and/or must be a bidimensional non-woven layer, so that the cells are grown only bidimensionally.

Appellants are definitely convinced that the Examiner has once again come to her conclusion on the basis of a further hindsight, while it is clear to Appellants that the skilled person would have had no reason to take Dorigatti et al. into consideration, nor even to combine the same with Valentini et al. in order to achieve the claimed invention.

Therefore, Appellants emphatically disagree with the Examiner, who affirmed, at page 12, par. 25, of the outstanding Office Action, that:

> In response to Applicant's argument that the Examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning.

It is evident that the Examiner has, indeed, gone well beyond the actual disclosure of the prior art documents in order to arrive at the claimed invention having derived her knowledge of the claimed invention solely from Appellants' disclosure.

Thus, since the defects and deficiencies of the primary reference to Valentini et al. have not, in any manner, been remedied by the secondary reference to Dorigatti et al., for at least the above reasons, the obviousness rejection has clearly been overcome and should be reversed.

4. Rejection under 35 U.S.C. §103(a) as being obvious over Valentini et al. (US 5,939,323) in view of Soranzo et al. (WO 96/33750)

Soranzo et al. disclose "artificial human skin comprising:

a) a microperforated membrane based on a hyaluronic acid derivative, on which keranocytes have been seeded and cultured,

b) an underlying non-woven tissue based on a hyaluronic acid derivative wherein fibroblasts have been seeded and left to proliferate" (see Claim 1)

that is used in dermatology, as a dermo-epidermal junction, in diagnostics, in the cosmetic field, for instance in hair grafting; in sum, for external purposes only.

Soranzo's artificial human skin is deemed to meet the following requirements, as listed at page 3, lines 3-11:

"1) their surfaces must allow for adhesion and cell growth;

2) neither the polymers themselves, nor their degradation products should cause inflammation or toxic phenomena when implanted *in vivo*;

3) the product should be perfectly reproducible in its three dimensions;

4) its ideal porosity is 50%, which gives a large surface area for cell-polymer interactions, sufficient volume for the deposit of extracellular matrix and only slight, or no, migrational impediments during *in vitro* culture."

Therefore, the teaching of Soranzo et al. as a whole is definitely different and readily distinguishable from the very particular teaching of Soranzo et al. employed by the Examiner which, once again, has arbitrarily been decontextualized by the Examiner. As a matter of fact, once again, the cell growth is taught to require three dimensional matrixes having a porosity of preferably 50%, so that a perfectly functional dermo-epidermal junction is obtained (page 4, lines 8, and page 5, lines 5-10).

Therefore, even in this case, Appellants wonder why the ordinary skilled person would have contemplated combining Valentini et al. with Soranzo et al., when the latter clearly does not pertain to the field of endeavour of the invention, and even why the hypothetical combination of the teaching of a 3-D scaffold having interconnected pores and the teaching of artificial human skin where the fibroblasts are grown on 3-D non-woven tissue, would result in a bidimensional membrane!

The Examiner deems Soranzo et al. to be a relevant document Laserskin® is used as microperforated membrane in the artificial human skin. However, it should be noted as follows:

1- said membrane is not used as such, but is always coupled with a 3-D non woven tissue to form the final product to be used for external purposes;

2- keratocytes are grown on said membrane, whereas fibroblasts are grown on the 3-D non woven tissue; and,

3- all of the requirements/advantages which the final product must meet are only ascribable to the 3-D structure, as indicated above.

Therefore, why would the skilled person have been motivated to take this document into consideration, as it does not even pertain to the field of endeavour of the claimed invention? And where is there even a suggestion to combine the two documents, when both the teachings, either alone or taken together, go expressly and exclusively in the direction of 3-D structures?

In view of the above, Appellants are absolutely convinced that the Examiner once again has come to her conclusions on the basis of a further hindsight, while it is clear that the skilled person would have had no reason to take Soranzo et al. into consideration, nor even to combine the same with Valentini et al. in order to arrive at the claimed invention.

Thus, since the defects and deficiencies of the primary reference to Valentini et al. have not been remedied by the teachings of the secondary reference to Soranzo et al., for at least the above reasons, the obviousness rejection should be reversed, since *prima facie* obviousness has not been established by a preponderance of the evidence.

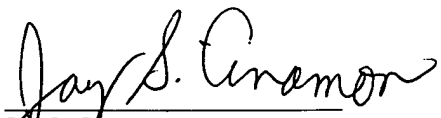
CONCLUSIONS

In view of the foregoing arguments as supplemented by Appellants' responses of record, the pending claims do not involve new matter and are not obvious under any of the three (3) § 103(a) obviousness rejections. Appellants respectfully request that the rejections be reversed and that the Examiner be directed to issue a Notice of Allowance.

Please charge any fees which may be due and which have not been submitted herewith to our Deposit Account No. 01-0035.

Respectfully submitted,

ABELMAN, FRAYNE & SCHWAB
Attorneys for Appellant

By 
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